

## Human Microbiome and COVID-19 Conundrum

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); formerly known as 2019-nCoV, was identified as the causal agent of a cluster of pneumonia cases in Wuhan (COVID-19), a city in the Hubei Province of China in November 2019. The SARS-CoV-2-coronavirus (SARS-CoV-2) is the causative agent of the current novel Severe acute respiratory syndrome (COVID-19) pandemic. SARS-CoV-2 is a positive-sense single-stranded RNA virus that belongs to the family Coronaviridae, subfamily Coronavirinae and genus Betacoronavirus. The viral genome encodes 10 structural and non-structural proteins. Besides, SARS-CoV-2 utilizes the same cell entrance point receptor-angiotensin converting enzyme II (ACE2)-as SARS-CoV. ACE2 receptor is a protein that is located on the surface of numerous types of cells in the human body, these include in the heart, gut, lungs and nose cells. This virus causes respiratory infection with mild to severe symptoms that can include pneumonia, dyspnea, hypoxia, respiratory failure, shock, or multiorgan dysfunction and death in 2.3% of infected. It was observed that a substantial percentage of cases develop severe and uncontrollable inflammation that is unable to control the infection and can lead to sepsis, multiorgan failure, and even death. Besides, SARS-CoV-2, infected individuals could exhibit symptoms such as vomiting and diarrhea and abdominal pain throughout the early phases of COVID-19 infection. COVID-19 infections demonstrate exceedingly variable response according to the pathophysiological situation of the host but with a lower morbidity in comparison with both SARS and MERS infections. The progress achieved in metagenomic next-generation sequencing (mNGS) technologies permitted the investigation of infectious agents directly from original clinical isolates. DNA-based NGS approach has paved the way for understanding pathogen identification abundance and genomic information, however, RNA-based mNGS approach could simultaneously reveal the entire “infectome” (i.e. RNA and DNA viruses, bacteria, yeasts and even parasites). Furthermore, RNA sequencing allows further valuable information beyond pathogen identification such as, pathogen abundance, full genome sequence, and specific gene(s) qualitative and quantitative expression. A conceivable target is of investigation is the respiratory microbiome represented as the composite microbial communities that enclose the respiratory epithelium and perform a vital role in modulating host immunity. In fact, several lines of evidence recommended the pharyngeal/ENT microbiomes as a possible target for alleviating the burden of respiratory viral infections.

Moreover, it was found that digestive symptoms are common in patients with COVID-19. Also, it was observed that patients that exhibit digestive complications have a longer period between the onset admission and their prognosis in comparison with patients without digestive complications. Additionally, physicians should diagnose digestive complications, such as diarrhea, as a characteristic feature of COVID-19 infection, and that the suspicion of contracting the disease should be elevated earlier in at-risk patients exhibiting digestive symptoms and not waiting for respiratory symptoms to appear.

Moreover, some COVID-19 patients exhibited digestive symptoms rather than respiratory symptoms.

Besides, it was found that as the sternness of the disease increased, digestive symptoms became more noticeable and patients without digestive complications will be more probable to achieve recovery and cleared from the hospitals in comparison with patients with digestive manifestations. All the previous findings emphasize the relation between COVID-19 infection, time from onset to admission and

prognosis, the severity of symptoms, and disease outcome. It was found that the mean interval of 9.1 - 12.5 days between the commencement of the disease and hospitalization. This postponement in the development to serious disease indicates that the pathogenesis of COVID-19 goes through a viral/host interaction processes, including host immune response/modulation. Finally, a single report stated that some patients with COVID-19 presented intestinal microbial dysbiosis with an obvious reduction of probiotic genera such as *Lactobacillus* and *Bifidobacterium*. Microbial communities are omnipresent and inhabit almost all identified ecological niches. These communities are ever-changing, vastly complex, and divergent. The microbial entities in these communities are regularly communicating and interrelating mutually, synergistically, and in numerous times competitively. Regardless of these inconsistent relationships, microbial communities typically reach a balanced relationship among their elements that ensure their stability and survival. It is well known that age, gender, immunosuppression, and comorbidities affect the outcome of COVID-19 infection, i.e. the degree of the severity of the disease. However, the main conundrum of COVID-19, the exceptions of the well-known risk factors, such as age, were observed. The gut microbiome plays important role in maintaining the integrity of the intestinal mucosal barrier, antagonistic effects against gut pathogen by both competing for the same nutrients and production of antimicrobial molecules against the pathogenic bacteria, fighting pathogen colonization, and stimulating the production of mucus to protect intestinal cells from attacks and avoid harmful effects of bacterial toxins and other hazardous components. Also, it was found that gut microbiota plays an important role in the maturation of the digestive tract, and in particular on the size and density of the gut mucosa, the production of mucus, the irrigation of intestinal cells, and the enzymatic activity of the mucosa. Most importantly, the gut microbiota is very necessary to induce and instruct the immune system, regulating locally and systemically, the activity of leukocytes and lymphocytes. Furthermore, recent studies have identified additional functions for the gut microbiota. Some bacteria of the gut flora may protect against inflammatory and metabolic diseases while others may induce these ailments or even behavioral and neurological disorders. A healthy gut microbiota creates a robust partnership with the host's intestines in a bi-directional way (symbiosis) and executes important functions such as the digestion of some nutrients (fermentation) and energy balance homeostasis. This important fermentation processes produce gas and numerous metabolites, including short-chain fatty acids (SCFA), butyrate, propionate, and acetate, that function as a fuel for the intestinal cells in the gut and also as signaling molecules in both gut and extraintestinal tissues. Any disturbance of this balanced system, dysbiosis, can cause disruptions affecting various areas of the human body and is associated with numerous human ailments. Gut microbiome alterations and its corresponding leaky gut epithelial barrier are associated with obesity, heart disease, chronic kidney disease, rheumatoid arthritis, non-alcoholic fatty acid disease, and depression. Several factors can cause gut microbiota dysbiosis such as lifestyle modifications, stress and sleep deprivation, uneducated antibiotic usage, immune system alterations, damages in the intestinal mucosa, loss of microbial diversity, increase of oxidative stress, bacteriophages, or the production of bacterial toxins and bacteriocins. There are five ways to restore the equilibrium of microbiota safely correct their imbalance (dysbiosis), namely, probiotics, prebiotics, synbiotics treatments, dietary intervention, and Fecal microbiota transplant (FMT). Unquestionably, age, and metabolic ailments such as obesity and type 2 diabetes are foremost risk factors for COVID-19 severity. Investigations on microbiota profile amongst lean and obese individuals showed that found that obese and nonobese subjects had dissimilar gut microbiota structures and compositions and that specific bacterial species were significantly associated with each group. Additionally, the ratio Firmicutes/Bacteroidetes (F/B) was higher in obese subjects and overweight subjects (BMI > 25). Besides, a similar increase was associated with increased fasting blood glucose levels. Additionally, the compulsory antibiotic treatment and dietary modifications administered to the severely affected COVID19 patients can aid in the gut microbiota dysbiosis. In fact, some hospitals in the US and UK called for improving the food environment for their COVID-19 patients by removing all sugary drinks from its vending machines and cafeterias and offering low-carb or sugar-free meals to its patients with diabetes. Restraining dietary carbohydrates is a successful intervention to improve glycemic control that can be implemented to improve the COVID-19 infection outcomes since the impaired metabolic function is one of the important COVID-19 morbidity and mortality risk factors. Therefore, I believe that gain a deep understanding of the expected dysbiosis occurs in both lung and gut during infection and changes in the infectome and microbiome and correlating this information with clinical information, the severity of infection, disease complication, and the outcome is of great importance to solve the COVID-19 conundrum. Suggested SARS-CoV-2/microbiome/host interactions include epithelial destruction and barrier dysfunction caused

by SARS-CoV-2 binding to ACE2 receptors on gut epithelial cells and co-occurring ailments such as aging, T2DM, obesity, and heart disease. Also, these interactions along with the induced dysbiosis lead to uncontrolled/un-advantageous innate immune activation and suppression of the adaptive immune response. Especially in the events of cases of severe disease of COVID-19, it is the innate response and not the adaptive immune response via T-cells that result in morbidity and mortality. Therefore, probiotics, prebiotics, synbiotics treatments, dietary intervention in elderly and diabetic or obese patients may well influence gut microbiome dysbiosis, short-chain fatty acid production, affecting immune homeostasis, barrier function, reduce the severity of COVID-19 and improve the disease outcome. Even though SARS-CoV-2 has been shown to infect the gastrointestinal tract and may be excreted and transmitted through stool, the ear, nose, and throat (ENT) microbiota might also play a vital role in accelerating COVID-19 pathogenesis. Therefore, a plausible target is the respiratory tract microbiome that envelopes the respiratory epithelium and plays a vital part in influencing host immunity. Several investigations suggested that the nose/throat microbiome may be a potential target for reducing the burden of respiratory viral infections. The lung commensal microbiota attunes interferon production in the lung, and it has been confirmed that the microbiota affects TLR-enhanced immune responses in the animal model of the cytokine storm. Interestingly, half of the general population has a T-cell response to SARS-CoV-2 due to cross-reactivity to common cold viruses which explains not only the large numbers of asymptomatic carriers of the virus but also the high degree of variation in the severity of COVID-19 amongst patients. There is no doubt that understanding gut, ENT, and respiratory microbiome dynamics and interaction with/within the host during the COVID19 infection, especially the immune responses, can help in the prevention and/or reduction of COVID19 infection complication, particularly amongst the high-risk groups. This is why many scientific groups, including ours, are focusing on the investigation of this important conundrum.

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